Outcomes of a Clinical Pathway to Standardize Use of Maintenance Intravenous Fluids

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ABSTRACT

OBJECTIVES: Improper use of maintenance intravenous fluids (IVFs) may cause serious hospital-acquired harm. We created an evidence-based clinical pathway to guide providers on the indications for IVF, its preferred composition, and appropriate clinical monitoring.

METHODS: Pathway implementation was supported by the creation of an electronic order set (PowerPlan) and hospital-wide education. Outcomes were measured among pathway-eligible patients for the years before (July 1, 2014–June 30, 2015) and after (July 1, 2015–June 30, 2016) implementation. An interrupted time series analysis was used to evaluate monthly trends related to IVF use, including the following: median duration, proportions of isotonic and hypotonic IVF, adherence to monitoring recommendations, incidence of associated severe dysnatremia, potassium-containing IVF use in the emergency department, and costs.

RESULTS: There were 11,602 pathway-eligible encounters (10,287 patients) across the study. Median IVF infusion hours did not change. Isotonic maintenance IVF use increased significantly from 9.3% to 50.6%, whereas the use of any hypotonic fluid decreased from 94.2% to 56.6%. There were significant increases in daily weight measurement and recommended serum sodium testing. Cases of dysnatremia increased from 2 to 4 among pathway-eligible patients and were mostly associated with hypotonic IVF use. Patients in the emergency department had a significant increase in the number of potassium-containing IVF bags (52.9% to 75.3%). Total hospitalization and laboratory test costs did not change significantly.

CONCLUSIONS: This is the first report of outcomes of a clinical pathway to standardize IVF use. Implementation was feasible in both medical and surgical units, with sustained improvements for 1 year. Future improvement work includes increasing PowerPlan use and developing clinical assessment tools.
In the past decade, the standard approach to pediatric maintenance intravenous fluid (IVF) therapy has shifted. For generations, the Holliday-Segar method (published in 1957 and based on studies of the caloric expenditure of previously healthy hospitalized infants) has been the standard for the composition and rate of IVF in pediatric patients of all ages. Despite the authors’ disclaimers that their calculations may not be generalizable, the most prominent concern raised about the Holliday-Segar method has been the risk of iatrogenic hyponatremia with hypotonic IVF; which can have devastating clinical consequences, including seizures, cerebral edema, and death. This risk is exacerbated in inpatients who commonly have 1 or more nonosmotic risk factors for increased antidiuretic hormone (ADH) secretion, including but not limited to the following: nausea, vomiting, uncontrolled pain, recent surgery, and acute respiratory and central nervous system disorders. Authors of a Cochrane Collaboration systematic review and meta-analysis concluded that isotonic IVF decreased the risk of hyponatremia by 52% compared with hypotonic IVF using data from 10 studies (pooled risk ratio = 0.48; 95% confidence interval [CI]: 0.38 to 0.60).

One clinical pathway related to IVF management in children has been previously described. To our knowledge, no article regarding the clinical outcomes of such a pathway has been published. In addition, we are unaware of any analyses related to the costs associated with pathway-guided IVF use.

We designed and implemented a clinical standard work (CSW) pathway to guide maintenance IVF use at our children’s hospital. Our specific aims with this study were to evaluate the pathway’s impact on the following: overall IVF use, use of isotonic and hypotonic IVF and potassium-containing IVF in the emergency department (ED), weight and laboratory monitoring, and incidence of severe dysnatremia.

**METHODS**

**Setting and Context**

There were sentinel events at our tertiary, 370-bed, university-affiliated children’s hospital and regional referral center that sparked an initiative to standardize use of maintenance IVF. A child with acute gastroenteritis who received more than the maintenance rate of hypotonic IVF developed severe iatrogenic hyponatremia and cerebral edema. Two other patients died of unrecognized hypernatremic dehydration because of inappropriate fluid restriction and inadequate clinical and laboratory monitoring. After these events, hospital leadership requested that a standardized approach be created to address inconsistencies and potential high-risk practices around IVF use. We formed a multidisciplinary team to design, implement, and monitor the maintenance IVF pathway. This team was led by faculty from general pediatrics and hospital medicine and included physician and nursing representation from emergency medicine, nephrology, and general surgery. The team was supported by a centralized clinical effectiveness group, which included a medical librarian, informatician, consultant, project manager, and data analyst.

**Interventions**

**Literature Review**

The standardized planning and implementation of our hospital’s CSW pathways has been previously described. A systematic literature search from 2004 to 2014 was undertaken using the search terms and selection process referenced in our publicly available pathway.

**Evidence Synthesis and Pathway Creation**

As evidence was synthesized, specific recommendations were developed (Supplemental Fig 4), and a pathway framework was created with phases for IVF initiation and monitoring. When evidence could not sufficiently address clinical questions, team members polled their respective colleagues and reported back to the group, with final decisions made using a Likert scale–based consensus tool. Using standard processes and templates developed by our hospital’s Clinical Effectiveness team, we developed a clinical algorithm with an associated web-based training module. Presentations were given to our hospital’s Clinical Standards Committee, Executive Nursing Leadership, and the Medical Director of Laboratories to establish wide-ranging awareness and support for our work. Key drivers were identified for each aim; an example for the use of potassium-containing IVF in the ED is included in Fig 1.

**Pathway Implementation and Logistical Support**

A maintenance IVF PowerPlan (Cerner Millennium; Cerner Corporation, London, UK) was created and embedded into all PowerPlans that previously contained IVF orders. The PowerPlan can also be ordered on its own. Informaticians assisted with the development of a weight change calculator that displays on the “patient summary” page of the electronic medical record and indicates both the absolute and relative (percentage) change between the last 2 consecutive measured weights. This allows for rapid identification of significant weight and/or fluid status changes in patients, defined as a difference of ≥3% and chosen based on conventional dehydration classification schemes and to ensure early identification of weight changes.

Patients are pathway eligible if they are euvoletic and require maintenance IV fluids on the basis of clinical judgment and are ineligible if they are any of the following: hypovolemic, hypervolemic, critically ill, on parenteral nutrition or a ketogenic diet, severely dysnatremic before IVF initiation (serum sodium ≥150 mEq/L or =130 mEq/L/40 weeks postmenstrual age, diabetic, or admitted to critical care or certain subspecialty services (nephrology, neurosurgery, cardiology, biochemical genetics, oncology, or organ and/or stem cell transplant). "Maintenance" is defined in our pathway as requiring ≥75% of fluid needs via IVF as calculated by the “4-2-1” rule, an hourly approximation of fluid requirements.

Providers are guided to select IVF composition on the basis of the presence or absence of increased ADH secretion risk factors. These include the following: uncontrolled pain, uncontrolled nausea and/or vomiting, recent surgery, acute central nervous system disorders, and acute pulmonary diseases, particularly...
pneumonia. Our pathway encourages clinicians to use their judgment in determining eligibility for the pathway and subsequent IVF choice.

Pathway implementation occurred on July 1, 2015. Pathway details were communicated through hospital-wide announcements and presentations at faculty meetings and teaching conferences.

Before pathway development, standard practice in our ED had been to use only non–potassium-containing IVF. This often led to IVF bags being wasted when potassium-containing IVF were subsequently ordered after admission. Our literature review did not reveal much evidence on this topic; however, given our pathway’s exclusion criteria, we were confident that patients with contraindications to potassium would be excluded from the pathway. To support the recommendation that maintenance IVF should include potassium for eligible patients, IVF bags in the ED were restocked so that maintenance IVF bags without potassium chloride were removed from automated dispensing cabinets.

Education
A web-based training module was required training for a subset of faculty in general pediatrics, hospital medicine, and emergency medicine. Surgical and medical residents were encouraged (but not required) to complete the training.

Pathway descriptions were included in nursing bulletins and reviewed at daily nursing huddles for 2 months after implementation.

Measures
Aim statements were formulated before pathway implementation to inform the process metrics that are reviewed at quarterly improvement meetings.

Objective 1
Our first objective was to determine if pathway implementation significantly reduces the overall use of IVF among pathway-eligible medical and surgical patients.

Aim Statement
Our aim was to decrease IVF use among pathway-eligible patients by 10%.

Outcomes

Duration of IVF was measured by the number of hours of IVF infusion at any rate >5 mL/h, as recorded by nurses. This cutoff rate was used on the basis of institutional policy for standard “to keep open” IVF rates. To assess for potential confounding by ICU stay, the proportion of pathway-eligible patient encounters with any time in the ICU and the mean length of ICU stay in days were compared pre- and post-pathway implementation. Each patient’s medical complexity was categorized by using the Pediatric Medical Complexity Algorithm.13

Objective 2
Our second objective was to assess whether pathway implementation significantly changes the frequency with which hypotonic (0.45% sodium chloride and 0.225% sodium chloride) and isotonic (0.9% sodium chloride) IVF are prescribed by providers and any resultant changes in the incidence of severe hyponatremia and hypernatremia.

Aim Statement
Our aim was to increase the use of isotonic fluids by 20%, with an equivalent decrease in use of hypotonic fluids.

Outcomes
The proportions of hypotonic and isotonic IVF orders were analyzed before and after implementation in pathway-eligible patients. This analysis was independent of the dextrose content of IVF because dextrose is rapidly used by cells and does not significantly contribute to intravascular osmolality compared with sodium and chloride. A chart review of pathway-eligible patients with severe hyponatremia and hypernatremia (sodium ≤130 or ≥150 mEq/L, respectively) was performed to better understand the clinical characteristics and potential risk factors associated with these electrolyte disturbances. The overall dysnatremia rate for this subgroup was calculated as follows: IVF-associated dysnatremia divided by all pathway-eligible patients on IVF.
**Objective 3**
Our third objective was to assess whether pathway implementation reduces waste and variability in maintenance IVF use by increasing the percentage of potassium-containing IVF bags ordered in the ED.

**Aim Statement**
Our aim was to have 80% of pathway patients receiving IVF in the ED to receive potassium-containing fluids at initiation.

**Outcomes**
The proportions of potassium-containing and potassium-free IVF bags were analyzed before and after implementation in pathway-eligible patients.

**Objective 4**
Our fourth objective was to determine if pathway implementation significantly improves appropriate clinical and laboratory monitoring for patients who remain on maintenance IVF.

**Aim Statement**
Our aim was that among patients on our pathway receiving maintenance IVF, 50% would have (1) daily weight measurement and (2) serum sodium checked within 36 hours of IVF initiation.

**Outcomes**
To measure adherence to the recommendation for daily weight measurements, we measured the number of patients on our pathway with a weight recorded per calendar day (numerator) divided by the total number of pathway eligible days (denominator). This calculation was then compared pre- and post-pathway implementation. To exclude patient weights and laboratory values obtained on admission, we only included pathway-eligible patients who had been on IVF for ≥12 hours. Additionally, a serum sodium result had to have been obtained <36 hours after first IV bag administration. This 36-hour mark reflects the PowerPlan, in which a serum sodium test is ordered for the subsequent bag administration. This 36-hour mark was estimated using $t$ tests for the mean of continuous variables, $\chi^2$ tests for categorical variables, and Wilcoxon rank tests for median of continuous variables when appropriate. An interrupted time series analysis was used to evaluate trends over time and compare pre- and post-pathway outcomes. Rates for each outcome were calculated per month. A linear regression was estimated for each time period, and Wald tests were used to compare slope parameters across periods and intercept parameters across periods.

**Ethics**
The hospital institutional review board approved this research project.

**Costs**
Costs were adjusted for inflation to 2016 dollars using the medical services component of the consumer price index and winsorized at the 99th percentile. Difference estimates for costs were calculated by using bootstrapped $t$ tests with 1000 replicates. Bias-corrected 95% CIs are reported.

**Analysis**
Outcomes were measured for the year before (July 1, 2014–June 30, 2015) and the year immediately after (July 1, 2015–June 30, 2016) pathway implementation. Population characteristics in both periods were compared by using $t$ tests for the mean of continuous variables, $\chi^2$ tests for categorical variables, and Wilcoxon rank tests for median of continuous variables when appropriate. An interrupted time series analysis was used to evaluate trends over time and compare pre- and post-pathway outcomes. Rates for each outcome were calculated per month. A linear regression was estimated for each time period, and Wald tests were used to compare slope parameters across periods and intercept parameters across periods.

**RESULTS**
In the year before pathway implementation, there were 6030 pathway-eligible encounters representing 5324 distinct patients. In the year after pathway implementation, 5572 encounters and 4963 distinct patients were pathway eligible. Pre-implementation, 68% of all admitted patients were pathway eligible compared with 63% post-implementation. The PowerPlan was used for 62% of all eligible encounters, totaling 3249 patients in the post-implementation period. There were no statistically significant differences in demographic characteristics, mean length of hospital stay, ICU admission rates, or medical complexity (Table 1) between the 2 study populations.

**Pathway outcomes are summarized in Table 2 and described in detail below.**

**IVF Use and Monitoring**
The median hours of IVF infusion in pathway-eligible patients was identical between study periods. The use of isotonic maintenance IVF increased significantly (9.3% to 50.6%; difference: 41.3%; 95% CI: 39.8% to 42.8%), whereas the use of any hypotonic fluid decreased significantly (94.2% to 56.6%; difference: −37.6%; 95% CI: −39.0 to −36.2%), as shown in Fig 2. The use of 0.225% saline (1/4 normal saline [NS]) accounted for a small percentage of IVF across study periods: 4% of eligible encounters in the pre-implementation period compared with 0.3% post-implementation.

**TABLE 1 Comparison of Pre- and Post-pathway Implementation Populations**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-implementation</th>
<th>Post-implementation</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathway-eligible encounters</td>
<td>6030</td>
<td>5572</td>
<td>—</td>
</tr>
<tr>
<td>No. distinct patients</td>
<td>5324</td>
<td>4963</td>
<td>—</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>7.9 (6.2)</td>
<td>8.0 (6.1)</td>
<td>.24</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>2685 (47.8)</td>
<td>2645 (47.5)</td>
<td>.69</td>
</tr>
<tr>
<td>Inpatient LOS, d, mean (SD)</td>
<td>3.4 (11.6)</td>
<td>3.2 (7.5)</td>
<td>.34</td>
</tr>
<tr>
<td>ICU admission, n (%)</td>
<td>451 (7.5)</td>
<td>391 (7.0)</td>
<td>.34</td>
</tr>
<tr>
<td>ICU LOS, d, median</td>
<td>1.6</td>
<td>1.6</td>
<td>.86</td>
</tr>
<tr>
<td>PMCA, n (%)</td>
<td>—</td>
<td>—</td>
<td>.08</td>
</tr>
<tr>
<td>Without chronic disease</td>
<td>2060 (34.2)</td>
<td>1820 (32.7)</td>
<td>—</td>
</tr>
<tr>
<td>Noncomplex chronic</td>
<td>1514 (25.1)</td>
<td>1493 (26.8)</td>
<td>—</td>
</tr>
<tr>
<td>Complex chronic</td>
<td>2454 (40.7)</td>
<td>2258 (40.5)</td>
<td>—</td>
</tr>
</tbody>
</table>

LOS, length of stay; PMCA, Pediatric Medical Complexity Algorithm; —, not applicable.
Compared with the pre-implementation period, during the post-implementation period there were significant increases in the number of potassium-containing bags administered in the ED (52.9% to 75.3%; difference: 22.5%; 95% CI: 19.4% to 25.6%; Fig 3) and the proportion of patients who had serum sodium monitoring within 36 hours of IVF initiation and a daily weight measurement.

**Severe Iatrogenic Hyponatremia and Hypernatremia**

Chart reviews of pathway-eligible patients with severe dysnatremia in the pre- and post-implementation periods revealed an increase in IVF-associated dysnatremia from 2 to 4 cases, respectively (Supplemental Table 3). No patients in the study required ICU transfer as a result of their dysnatremia.

**Costs**

The mean total costs of hospitalization did not significantly increase from pre- to post-pathway implementation (from $18,880 per encounter to $19,581 per encounter; difference: $701; 95% CI: −$108 to $1409). The mean costs of IVF per account increased significantly by $14. Mean electrolyte and serum sodium laboratory test costs per account were not significantly different.

**DISCUSSION**

To our knowledge, this is the first study of a clinical pathway in which an evidence-based approach to maintenance IVF therapy in medical and surgical pediatric patients is standardized. With our pathway, we have succeeded in changing and sustaining prescribing practices of clinicians away from hypotonic IVF and toward monitored use of isotonic IVF when there are concerns for increased ADH secretion. Although there are potential risks and harms associated with the use of IVF of any composition, the safety of isotonic fluids to meet maintenance hydration needs with significantly less risk for iatrogenic hyponatremia is supported by a growing body of evidence.2-4,8-9 Our CSW pathway demonstrates how evidence can be operationalized and is not a substitute for clinical research.

Systematic changes to promote consistent use of maintenance IVF between ED and acute care units led to a 22.5% increase in use of recommended potassium-containing IVF in the ED. We continue to see these changes sustained >1 year after pathway implementation, largely because the supply in ED dispensing cabinets was changed to ensure that recommended IVF bags are readily available. There have been no reports of pathway-associated hyperkalemia since implementation.

The median duration of IVF use, including infusion hours in the ED before admission, did not change pre- and post-implementation. There are no national benchmarks for IVF use to provide a point of comparison; however, future pathway efforts will reinforce appropriate IVF use only when enteral routes of hydration are not possible and prompt IVF discontinuation when feasible. Our post-implementation plan-do-study-act work includes discussions with pharmacy leaders to incorporate questions about IVF use as part of their standard work to encourage a paradigm shift to view IVF as a medication with serious risks.

During the creation and implementation of this pathway, our biggest challenge was formulating feasible recommendations for weight and sodium monitoring. Collaboration with nursing leadership to (1) provide ongoing education about the pathway’s monitoring recommendations and (2) address practical constraints (eg, availability of scales on every unit) has been essential in maintaining the gains in adherence to these recommendations.

The most controversial recommendation of our pathway has been serum sodium monitoring, the value of which has been questioned given the overall low incidence of severe iatrogenic dysnatremia in our population and the associated pain, anxiety, and costs of this test. This recommendation was based on our literature review and data showing that the incidence of iatrogenic

### TABLE 2 Outcomes Pre- and Post-pathway Implementation Among Pathway-Eligible Patients

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Pre-implementation</th>
<th>Post-implementation</th>
<th>Difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVF infusion, h, median</td>
<td>18.0</td>
<td>18.0</td>
<td>—</td>
<td>.19</td>
</tr>
<tr>
<td>IVF composition usage, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotonic (NS)</td>
<td>569 (9.3)</td>
<td>2819 (50.6)</td>
<td>41.3 (39.8 to 42.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypotonic (any)</td>
<td>5679 (84.2)</td>
<td>3155 (56.6)</td>
<td>−37.6 (−39.0 to −36.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1/2 NS</td>
<td>5484 (91.1)</td>
<td>3145 (56.4)</td>
<td>−34.7 (−36.1 to −33.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1/4 NS</td>
<td>284 (4.4)</td>
<td>15 (0.3)</td>
<td>−9.1 (−8.2 to −9.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ED IVF encounters with K-containing IVF, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>965 (52.9)</td>
<td>1204 (75.3)</td>
<td>22.5 (19.4 to 25.6)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Eligible patients with sodium level check, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>362 (18.4)</td>
<td>537 (30.5)</td>
<td>12.1 (9.4 to 14.8)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>% of eligible d with wt collected, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>47.9 (43.5)</td>
<td>55.6 (42.9)</td>
<td>7.8 (4.8 to 10.7)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Instances of dysnatremia</td>
<td>2</td>
<td>4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total costs (2016 $), mean (SD)</td>
<td>18879.8 (21002.1)</td>
<td>19580.6 (20789.9)</td>
<td>700.8 (−108.0 to 1409.1)</td>
<td>.07</td>
</tr>
<tr>
<td>Fluid costs (2016 $), mean (SD)</td>
<td>99.5 (106.4)</td>
<td>113.6 (121.4)</td>
<td>14.1 (10.1 to 18.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Electrolyte laboratory test costs (2016 $), mean (SD)</td>
<td>62.0 (86.1)</td>
<td>58.6 (71.8)</td>
<td>−3.4 (−8.1 to 2.0)</td>
<td>.20</td>
</tr>
<tr>
<td>Serum sodium laboratory test costs (2016 $), mean (SD)</td>
<td>15.9 (9.1)</td>
<td>15.6 (6.8)</td>
<td>−0.3 (−3.3 to 2.3)</td>
<td>.85</td>
</tr>
</tbody>
</table>

Differences represent differences in rates where rates are shown. Otherwise, it is the difference in means. Differences, 95% CIs, and P values are estimated using t tests or rank-sum tests for comparison of medians. K, potassium; —, not applicable.
Hyponatremia is highest among patients on IVF in the first 24 hours after initiation as well as discussions with multidisciplinary stakeholders. Our chart review of pathway-eligible patients revealed an increase in severe IVF-related dysnatremia between pre- and post-implementation periods (Supplemental Table 3), which could be attributed to greater detection after pathway implementation. Of the total 6 cases of severe dysnatremia across study periods, 4 occurred in patients with hyponatremia who had received hypotonic fluids. Two patients in the post-implementation period had hypernatremia; 1 patient presented with acute illness and mild hypernatremia (149 mEq/L) that worsened with isotonic IVF, and a second, medically complex patient had hypernatremia while receiving hypotonic IVF in the setting of missed enteral feedings and possible dehydration. These results are consistent with the pathophysiologic basis for our pathway recommendations and underscore the need for careful clinical assessment for increased ADH secretion risk factors for each patient.

We found that for every 2589 patient encounters, 1 instance of severe IVF-related dysnatremia occurred. This number needed to harm does not capture less severe dysnatremias and should be interpreted cautiously, especially because we identified cases retrospectively via electronic medical record. In randomized controlled trials in which researchers compared isotonic and hypotonic IVF, real-time standardized clinical assessment tools have been used to evaluate adverse effects such as hypertension and edema. A future area of intervention is to identify those at greatest risk of dysnatremia with such a tool and target serum sodium testing to these patients.

The financial costs of IVF increased significantly between pre- and post-pathway periods, although the absolute difference ($14; 95% CI: $10 to $18) was unlikely to have had clinical significance. Total hospitalization and laboratory test costs did not increase significantly between study periods, indicating that our pathway was not associated with significant cost increases.

Our study has additional limitations. We have had ~60% PowerPlan usage despite efforts up front to embed it into all major medical and surgical plans. This may be the result of providers ordering maintenance IVF after admission orders have already been placed, thus bypassing the full PowerPlan that includes IVF composition and monitoring recommendations. We currently rely on reporting and feedback by providers to identify plans that do not contain our PowerPlan, and this has caused a lag in addressing gaps in use. There is also a difference between medical and surgical units in PowerPlan use (53% on the medical unit and 78% on the surgical unit), which we are addressing as a targeted area for improvement. The generalizability of our results is limited because our pathway was
implemented and studied at a single, freestanding tertiary-care children’s hospital with a culture of patient safety and standardized pathways. Finally, the successes of this pathway work should be assessed for their value. We plan to conduct a formal value analysis for serum sodium testing using a previously published tool.14

CONCLUSIONS

The implementation of our clinical pathway has led to sustained changes in IVF-prescribing practices and improved consistency of IVF use between the ED and acute care units, adherence to weight and serum sodium monitoring recommendations, and evidence-based use of isotonic IVF.

Acknowledgments

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